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PRODUCTION OF STABLIZED INTERFERON PREPARATION
[ANTEINA INTAFERON SEIZAI NO SEIHO]

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Specification

1. Title of Invention

Production of Stabilized Interferon Preparation

2. Claim

1) A method of producing an interferon preparation characterized by adding an amino acid or an amino acid and human serum albumin to an interferon aqueous solution and then freeze-drying it.

2) A method of producing an interferon preparation as described in Claim 1 wherein the aminoacid is a polar aminoacid.

3) A method of producing an interferon preparation as described in Claim 2 wherein the polar aminoacid is glutamic acid.

3. Detailed Description of Invention

The present invention relates to a stabilized interferon preparation. It relates particularly to a method of production of interferon, characterized by adding an amino acid or an amino acid and human blood serum albumin to an interferon aqueous solution and freeze-drying it.

Interferon is a type of glycoprotein that is produced from animal cells including human cells by stimulating a virus or other substance and is a substance that is

extremely useful for its virus proliferation suppression action, an anti-[illegible] action and the like.

There are a number of types of interferon; these are classified broadly into types α, β and γ, and subtly different pharmacological effects can be expected from each.

However, none of these types of interferon required any special processing in order for it to be provided in the form of a drug, as it is unstable.

Thus far, a number of tests involving freeze-drying using a variety of prescriptions have been carried out to improve the stability. However, no satisfactory results were obtained, and it has been difficult to study these.

Besides carrying out research on refining human interferon, the inventors spent long years of research on a method of stabilizing the activity of these, they found

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surprising new information that, by adding an amino acid or an amino acid and human serum albumin to an interferon aqueous solution and freeze-drying it, the activity of the interferon in a freeze-dried state could be considerably stabilized, and they completed the present invention.

There is a considerable effect in the present invention even if an amino acid is used. However, using a polar amino acid is thought to be more effective.

This polar amino acid has been classified in [Physics of Enzymes] (Borgenstein, Hoichi Tanaka, trans., Mizuho Shobo Publishers, 1972). The work points out that the characteristics of the amino acids are hydrophilic on the whole and more specifically cites Arg, ASp (NH_2), Glu, Glu (NH_2), His, Lys, Ser, Thr and the like. Further, the salt of an amino acid, such as a sodium salt and the like, may be likewise used.

Furthermore, although there are no particular stipulations on the amount of amino acid to be added, it is appropriate to add 0.05 to 0.8 W/v %. Moreover, adding human serum albumin is not required, however, the stabilizing effect is confirmed even when it is coexistent. A suitable amount to be added at that time is thought to be 0.01 to 1 W/v %.

When carrying out the method in the present invention, an amino acid or an amino acid and human serum albumin is added to an interferon aqueous solution. Then, a method that involves adjusting the pH to approximately 7.1 ± 0.1 using hydrochloric acid and sodium hydroxide increases the stability of the interferon, making it suitable. Moreover,

although the solution obtained is freeze-dried, that method is the one usually used.

In carrying out the method in the present invention, an isotonizer, pH adjuster, analgesic, excipient and the like may be added using the regular method.

Separately, the inventors found that interferon was stabilized by adding glucose to the interferon aqueous solution. However, either the glucose aqueous solution is used for the solution in which the interferon freeze-drying agent obtained using the method in the present invention is dissolved, or the interferon can be stabilized after dissolving by adding glucose after dissolving using a physiological salt solution.

Next, we shall describe the present invention more specifically in the experimental examples.

Experimental Example

We added glutamic acid (added so that the final concentration was 0.2 W/v %), glucose (likewise so that the final concentration was 1 W/v %), and mannitol (likewise so that the final concentration was 1 W/v %) respectively to a human interferon solution (containing interferon-n in 1.6 x 10^6 international units in 1 ml), in which the human serum albumin was added at a concentration of 0.15 W/v %. Then, we adjusted the pH to 7.1 ± 0.1 using 0.1 N-Hcl and 0.1 N-

NaOH, filtered it, freeze-dried it, filtered the abovementioned human interferon solution (pH of 7.1 ± 0.1) as is as a control, and we compared the stability for the one that had been freeze-dried.

Furthermore, we measured the potency of the interferon using the RIA(Note) method using a monoclonal antibody of the interferon.

Results are indicated in Table 1. In adding the human serum albumin and glucose, a pronounced decline was observed in the coloring as well as the potency and the pH. Moreover, even in the human serum albumin, the sample with added mannite, and the sample to which only the human serum albumin had been added, a decline in the potency was confirmed. On the other hand, in the human serum albumin and the same with glutamic acid added, there were no problems whatsoever in the potency, pH, characteristics and state.

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Table 1

A	Section	B	C	D	E
At start	F	100	100	100	100
	G	white	white	white	white
	H	colorless, clear	colorless, clear	colorless, clear	colorless, clear
	I	7.25	7.15	7.09	7.08
50°C 2 weeks	F	84.8	98.5	25.6	78.1
	G	no change	no change	brown	no change
	H	no change	no change	brown, clear	no change
	I	7.87	7.18	3.75	7.18
50°C 4 weeks	F	64.8	100.5	--	65.1
	G	no change	no change	dark brown	no change
	H	no change	no change	dark brown, clear	no change
	I	7.36	7.15	3.28	7.20

A: coexistent conditions

B: human serum albumin added

C: human serum albumin and glutamic acid added

D: human serum albumin and glucose added

E: human serum albumin and mannite added

F: potency

G: characteristics

H: state

I: pH

(Note) The potency is indicated by the relative amount when the potency at the start of coexistence is 100.

(Note) RIA using interferon α monoclonal antibodies; interferon α kit made by Dynabbott RI Research Institute used

Next, we shall provide practical examples of the present invention, although it should by no means be construed that the present invention is limited to these.

Practical Example 1

We added glutamic acid with a final concentration of 0.2 W/v % to a human interferon solution (containing interferon α in 1.6×10^6 international units in 1 ml) and adjusted the pH to 7.1 ± 0.1 using 0.1 N-Hcl and 0.1 N-NaOH and filtered it. We freeze-dried this and obtained a stable human interferon α preparation.

Practical Example 2

We added human serum albumin and glutamic acid to a human interferon solution (containing 1.6×10^6 international units of interferon α in 1 ml) so that the final concentration was 0.15 W/v % and 0.2 W/v %. We adjusted the pH to 7.1 ± 0.1 using 0.1 N-HCl and 0.1 N-NaOH and filtered it. We freeze-dried this and obtained a stabilized human interferon α preparation.